REMARKS

Applicants acknowledge the Advisory Action mailed August 26, 2008 and respond herein to the Advisory Action and the Final Rejection mailed June 12, 2008. The present Amendment constitutes a submission to accompany a Request for Continued Examination in the present prosecution. Entry of the present Amendment and allowance of the pending claims is respectfully requested.

Claims 1 and 17 have been amended to include the subject matter of original claim 20 and elements of paragraph 0043 of the published application. Support for these amendments can be found in claim 20 as originally filed and in the specification at paragraph 0021, 0031, 0043 and Figs. 1 and 3. Claim 20 has been cancelled. No new matter has been added.

In paragraphs 4-18 of the Office Action mailed June 12, 2008 the Examiner rejected claims 1 and 3-21 under 35 USC 103(a) as being obvious over CAB8-Computer Applications in Biotechnology, June 25-27, 2001 (hereinafter "Cornelissen et al.") in view of United States Patent No. 5,346,826 (hereinafter Andrews).

Reconsideration is requested.

Cornelissen et al discloses a method for production of recombinant proteins. However, Cornelissen does not teach a method or device that employs a second harvest receptacle (18) for a cell-contaminated harvest of the retentate that is connected to the bioreactor (1) by way of a harvest line (19). Furthermore, Cornelissen et al. does not disclose a method or device comprising a control unit containing an analytical system that measures cell concentration using a sensor in the bioreactor, wherein the control unit can control the cell concentration in the bioreactor by controlling a harvest pump upstream from a second harvest receptacle. Additionally, Cornelissen et al. does not disclose that method or device by which the sensor in the bioreactor measures the cell concentrate, namely through the use of analyzer (41) a regulator (42) and a reference operator (43).

The Examiner has stated that "Cornelissen teaches that the cell concentration is measured by a sensor (Fig. 4-BIOSTAT ED) which is configured to a controller or computer...[and] that sensors and a controller are connected to feed pumps, but remains silent regarding a pump up stream of the second harvest vessel or holding tank".

Applicants submit that the section of Cornelissen et al the Examiner points to only discloses that a bioreactor is monitored by equipment with computer controls. It does not specifically disclose that the cell concentration in the bioreactor is being measured by a system that is linked to a harvest pump which can adjust the cell concentration in the bioreactor by withdrawing cell concentrate to a second harvest receptacle, and it does not disclose the use of a regulator or a reference operator to measure the cell concentrate.

To alleviate some of the deficiencies in Cornelissen et al the Examiner points to Andrews, and specifically pump P62, for additional support for a system that controls the amount of cell concentration in the bioreactor. However, Applicants submit that the pump P62 is not an equivalent of the harvest pump (20), nor does it render obvious the use of the harvest pump (20) of the present invention. The pump P62 of Andrews is used for recycling cells to the bottom of the bioreactor B5 from the holding tank HT15 (*see* Andrews at Fig. 2, and col. 13, line 5 to col. 14, line 8). The holding tank HT15 is used to "grow the cells to a greater size and weight before the cells are centrifuged or separated". *Id.* In contrast the harvest pump (20) in the present invention is only used for withdrawing cell concentrate from the bioreactor and moving it to the second harvest receptacle (18). This is a one way flow that only removes cell concentrate from the bioreactor, it does not return cell concentrate back to the bioreactor (1) and does not remove it for further cell growth. Further, Andrews does not disclose that the harvest pump is controlled by an analytical system comprising a sensor in the bioreactor that measures cell concentration and specifically adjust cell concentration by use of harvest pump upstream from a second harvest receptacle. The storage tank HT15 of Andrews is more akin to the first harvest receptacle (16) of the present invention, not the second harvest receptacle (18), in that permeate is recycled to the bioreactor (1). There is no relation between the storage tank HT15 of Andrews and the second harvest receptacle (18) of the present invention.

Additionally, the Examiner stated in paragraph 3 of the Office Action that "it would be an obvious modification to tap the retentate line to include a three way valve to alter the flow between the bioreactor and a second harvest vessel". Applicants respectfully disagree. The present invention would not achieve the intended results by providing a three way valve from the retentate line (17) and splitting the feed between the first harvest receptacle (16) and the second harvest receptacle (18). In contrast the

present invention provides two separate systems which remove medium from the bioreactor. A conveying line (13) moves medium to the downstream cross-flow filtration unit (5), which can then either pump the medium along a retentate line (17) back to the bioreactor (1) or along permeate line (15) to the first harvest receptacle (16). Separately, harvest line (19) runs from the bioreactor (1) to the second harvest receptacle (18). The retentate line (17) runs from the downstream cross flow filtration unit (5) back to the bioreactor (1), whereas the harvest line (19) runs from the bioreactor (1) to the second harvest receptacle (18) (*see* the present specification at Fig. 1 and paragraphs 0029-0032). Therefore it would not have been obvious, or possible, to simply tap the retentate line of Cornelissen et al. to achieve the dual harvest receptacle configuration of the present invention, especially, where the permeate moves alternately from a downstream cross-flow filtration unit (5) to either the first harvest receptacle (16) or back to the bioreactor (1).

Further, when the authors of Cornelissen et al. sought to remove waste or, cell contaminated harvest from the system, the waste was separated from the first harvest receptacle by an ultra filtration device and placed in a waste container (*see* Fig. 1 of Cornelissen et al.). The waste was not separately removed directly from the bioreactor, but from the first harvest receptacle. This is not the same method as recited in the claims of the present application.

Andrews is also cited for its teachings regarding the use of a holding tank for storing cultivated cells before being separated by a centrifuge and/or being returned to the bioreactor for further growth. However, the holding tank (HT15) of Andrews would be more analogous to the first harvest receptacle (16) of the present invention (if it were analogous to any portion of the present invention) and not to the second harvest receptacle (18). This is because the medium flowing from the bioreactor (1) only returns to the bioreactor (1) from the first harvest respectable (16) along retentate line (17), and not reversely from harvest line (19) and the second harvest receptacle (18).

Because neither Cornelissen et al., nor Andrews teach or suggest: (A) a control unit containing an analytical system that measures cell concentration using a sensor in the bioreactor, wherein the control unit can control the cell concentration in the bioreactor by controlling a harvest pump upstream from a second harvest receptacle, and wherein said harvest pump only withdraws cell concentrate from said bioreactor; or (B) the use of a

second harvest receptacle for storing cell contaminated retentate, wherein said second harvest unit is connected to the bioreactor by dedicated lines separate from the downstream cross-flow filtration unit (5) and the first harvest receptacle (16); it is requested that the 103(a) rejection be withdrawn.

In paragraphs 19-21 of the Office Action mailed June 12, 2008 the Examiner rejected claim 2 under 35 USC 103(a) as being obvious over Cornelissen et al. in view of Andrews and further in view of United States Patent No. 5,403,479 (hereinafter Smith et al.).

Reconsideration is requested.

As discussed above, Cornelissen et al. and Andrews do not teach or suggest each and every element of amended claim 1 of the present application. Additionally, Applicants submit that Smith et al. does not alleviate the deficiencies that exist in Cornelissen et al. and Andrews. Smith is cited for its teachings regarding cleaning of membranes using cleaning solutions and biocidal solutions. These teachings do not alleviate the deficiencies with regard to claim 1, namely the lack of a second harvest receptacle for storing cell contaminated retentate connected to the bioreactor along dedicated lines and the lack an analytical system for measuring cell concentrate in the bioreactor and removing said cell concentrate by use of a harvest pump and a second harvest receptacle. Therefore Applicants submit that Claim 2 of the present invention is not obvious in view of the cited prior art and it is requested that the 103(a) rejection be withdrawn.

Based upon the above amendments and remarks, Applicants respectfully submit that claims 1-19 and 21 are allowable over the prior art and that the present application is in proper form for allowance.

Favorable consideration and early allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

Anthony J. Casella, Esq.
Reg. No. 24,095
Customer No. 001218
CASELLA & HESPOS LLP
274 Madison Avenue-Suite 1703
New York, NY 10016
Tel. (212) 725-2450
Fax (212) 725-2452

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